Original Article

Adverse Drug Events in Patients with Mental Disorder in an Ambulatory Setting

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Abstract

Background: Although adverse drug events (ADEs) among inpatients occur frequently and are widely studied, few data are available on ADEs among outpatients with mental disorders. **Aims:** To determine the rates, types, and severity of ADEs in patients with mental disorder. **Materials and Methods:** Cross-sectional survey of patients with mental disorder attending outpatient department. Data were collected over a period of 6 months. **Results:** A total of 400 patients (217 schizophrenia patients, 127 bipolar affective disorder patients, and 56 patients of depression) with a mean age of 32.1 ± 9.7(±standard deviation) participated in the study. Patients suffering from schizophrenia and all nonadherent patients reported significantly more ADEs ($P < 0.05$). Out of 343 patients (86%) who reported at least one ADE, majority (87%) reported central nervous system ADEs followed by weight gain (48%), gastro-intestinal (28%), skin (4%), cardiovascular (1%), and sexual dysfunctions (0.3%). Out of 673 ADEs reported, sedation (41%) and weight gain (25%) were reported most commonly. Most ADEs reported (76%) were mild; however, there were no life-threatening, fatal, or serious ADEs. The medication classes most frequently involved in ADEs were antipsychotics (72%) followed by sedatives (44%), antimanic drugs (32%), and antidepressants (27%). Patients on atypical antipsychotic drugs reported significantly more body weight gain ($P < 0.05$). More than three drugs were prescribed in 49% of patients who reported ADEs. **Conclusion:** The study data indicate high prevalence of ADEs in the outpatients on psychotropic medications.

Keywords: *Adverse drug events, mental disorders, outpatients, pharmacovigilance*

Introduction

The adverse drug event (ADE) is an adverse outcome that occurs while a patient is taking a drug.[1] Since it is not always possible to attribute casualty, ADEs may not always be drug induced. ADEs are frequently reported from in patients in several studies.[2-4] According to the studies in the US, 6.5% of hospitalized patients had an ADE and 4.7% of all hospital admissions were because of ADEs.[2] According to a study, the cost of drug-related morbidity and mortality exceeded $177.4 billion in the year 2000 with drug-related mortality estimated to claim 218,000 lives.[5] Although most prescribing occurs in outpatients settings, there are only few studies reporting ADEs in the ambulatory setting.[6] There are several factors which make it difficult to identify ADEs among outpatients. These patients obtain and administer their own medications. Since contact with the psychiatrist is for a limited period, the patients may also infrequently communicate about their problems. Furthermore, there is inadequate documentation of outpatient records. Some studies estimate the proportion of outpatients with an ADEs range from 5% to 35%.[7,8] Although there are no reported prospective ADEs data in outpatients in psychiatric practice, some studies have determined that psychiatric medications account for a major proportion of ADEs in inpatients.[9] Furthermore, the new second generation or atypical antipsychotics and serotonin reuptake inhibitors have represented, especially important advances, but many of these drugs also have important adverse effects which need to be addressed.

Since there is a paucity of data on ADEs in outpatients in mental disorders in India, this study was done to identify and determine the rates, types, and severity of self-reported adverse events in the outpatients of a tertiary care psychiatric hospital in India.

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Materials and Methods

Study design

A cross-sectional survey of patients with mental disorders attending the outpatient department (OPD) at the Institute of Human Behaviour and Allied Sciences (IHBAS), a tertiary care mental health facility in North East of Delhi, was conducted over a period of 6 months from January to June 2009. The patients were selected randomly and were interviewed for any self-reported adverse events by the trained staff after written and verbal consent by the patient or their caretaker. Written informed consent from all the patients and necessary approval from the Institutional Ethical Committee were obtained.

Data collection

Data were collected and entered on a predesigned ADE reporting form over a period of 6 months from the OPD at the tertiary care hospital. Data were collected by trained staff of the Department of Psychiatric Social Work at the IHBAS, Delhi. Any relevant laboratory investigations results were also entered in the ADE reporting form. The diagnosis of the mental disorder was made after reviewing the OPD records made by the qualified psychiatrist.

Inclusion criteria

- Patients aged 18 years or above attending OPD of the tertiary care hospital
- Patients reported physician-diagnosed schizophrenia, bipolar affective disorder (BPAD), and depression.

Exclusion criteria

- Patients with severe mental disorder and aggressive/violent patients
- Patients with diagnosis of severe depression with currently suicidal ideation
- Patients with diagnosis of mental retardation
- Patients with diagnosis of any organic cause for his/her behavioral disturbance or organic brain syndrome.

Adverse drug events

All patients reported ADEs were analyzed. The ADEs were classified according to the severity and types. Severity of the ADEs was rated according to the patient's perspective.[10] Patient-stated severity of ADEs were categorized as mild (normal activities are unaltered or are annoying but tolerable and ADE not communicated to the psychiatrist); moderate (altered normal activities and ADE communicated to the psychiatrist for decrease in dose or its treatment); and severe (unable to undertake normal activities and ADE communicated to the psychiatrist for its treatment and change of therapy). Treatment adherence was also evaluated from the exit interviews and was ascertained by patient interview, leftover medicines, medicine refill interval, etc.[10] According to the adherence status, the patients were categorized as adherent (≤3 skipped doses in a month) and nonadherent (>3 doses skipped in a month).[11] Since no consensus definition for polypharmacy emerged during our literature search, we defined polypharmacy as a patient taking three or more drugs.[12]

Statistical analysis

Patients who reported ADEs to medication and those who did not report any ADEs were compared on patient characteristics such as demographics, treatment characteristics, and medications. Comparisons that used categorical variables were analyzed with Chi-square test. Results are presented as mean ± standard deviation or as percentage. $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS software version 17 (Chicago, IL, USA).

Results

A total of 400 patients, 238 (59.7%) males and 162 (40.3%) females) were enrolled and demographic characteristics are given in Table 1. The mean age of the patients was 32.1 ± 9.7 years. The majority were suffering from schizophrenia (54.3%), followed by BPAD (31.8%), and depression (14%). About 32% of the patients had no formal education.

Of the 400 outpatients who were surveyed 343 (86%), patients reported ADEs. Of 343 patients who reported at least one ADE, majority (87%) reported the central nervous system (CNS) ADEs followed by weight gain (48%), gastrointestinal (28%), skin (4%), cardiovascular (1%), and sexual dysfunctions (0.3%). A total of 673 ADEs were reported with the adverse event rate of 168 ADEs per 100 patients or ADE rate of 1.68 ADE per patient with a maximum of 6 ADEs in a patient. Among all types of ADEs, CNS ADEs were reported to be highest followed by body weight gain [Table 2]. Median duration of the mental illness was 61.5 months and was more than 3 years in 69% of the patients. However, the median total duration of treatment at a psychiatric care facility was 57 months. Out of 400 patients, 153 (38.25%) patients reported nonadherence. Significantly higher ADEs were reported in nonadherent patients [Table 3] and also in patients with schizophrenia [Table 1]. The mean number of medicines prescribed per day was 2.50 ± 0.94 [Table 3]. Out of 188 patients who were prescribed three or more than three medicines per day (polypharmacy), ADEs were reported in 48.7% of patients. There were no significant differences between the patient reporting ADEs and several other demographic characteristics such as age, gender, and education. Compared to other types of ADEs, more CNS ADEs (55%) were reported by the patients [Table 2]. Among the total number of ADEs, highest numbers (486 or 72%) were reported from the patients on antipsychotic drugs followed by sedatives (44%), antimanic drugs (32%), and antidepressants (27%) [Table 4]. Significantly more number of patients on antipsychotics reported ADEs (246 patients, $P < 0.05$). Furthermore,

Table 1: Patient demographics

	No ADEs‡ (*n*=57)	ADEs (*n*=343)	Total (*n*=400)	*P*
Age (year)				
Mean±SD (range)	31.3±10.4 (18-64)	32.2±9.6 (18-64)	32.1±9.7 (18-64)	
Gender (%)				
Male	38 (66.7)	200 (58.3)	238 (59.5)	0.23
Female	19 (33.3)	143 (41.7)	162 (40.5)	
Mental disorder (%)				
Schizophrenia	24 (42.1)	195 (56.9)	219 (54.8)	0.03*
Depression	6 (10.5)	47 (13.7)	53 (13.3)	
BPAD	27 (47.4)	101 (29.4)	128 (32)	
Education (%)				
No formal education	13 (22.8)	115 (33.5)	128 (32)	0.25
School education	34 (59.6)	182 (53.1)	216 (54)	
University education	10 (17.5)	46 (13.4)	56 (14)	

‡Patients not reporting any ADEs. BPAD: Bipolar affective disorder; ADEs: Adverse drug events; SD: Standard deviation; *Statistically significant $P < 0.05$

Table 2: Type of adverse drug events

Type of ADEs (*n*=673 ADEs)	Percentage
CNS ADEs - sedation, EPS, dizziness, ataxia, cognitive deterioration, lethargy, fatigue, anxiety, hyperactivity, depression, insomnia, tinnitus, headache, confusion	55.10
Body weight gain	24.50
GIT ADEs - nausea, vomiting, constipation, diarrhea, dry mouth, altered appetite	16.60
Skin rashes, urticaria, photosensitivity, sweating, SJS	1.90
Miscellaneous - urinary retention, palpitations, postural hypotension, menstrual disturbances, sexual dysfunctions, body weight loss, edema, and tremors	1.90

ADEs: Adverse drug events; CNS: Central nervous system; EPS: Extra pyramidal symptoms; SJS: Steven Johnson syndrome; GIT: Gastrointestinal tract

antipsychotic drugs were associated with all the major CNS ADEs (sedation, cognitive deterioration, and extrapyramidal symptoms (EPS).

There were no life-threatening, fatal, or serious ADEs reported. Among the patient stated severity of ADEs. Majority of the ADEs (75.6%) were mild. Only three severe ADEs (severe weight gain) were reported.

Among the CNS ADEs, sedation was reported in more than 74% of the patients followed by cognitive deterioration and EPS. Furthermore, sedation was reported in significantly higher number of nonadherent patients ($P < 0.05$). EPS were reported by only 25 (6.7%) patients. Out of 276 patients receiving antipsychotics, majority (190 patients or 69%) were

Table 3: Treatment characteristics

	No ADEs‡ (*n*=57)	ADEs (*n*=343)	Total (*n*=400)	*P*
Number of prescribed medicines/day				
Mean±SD (range)	2.25±0.87 (1-5)	2.55±0.95 (1-6)	2.5±0.94 (1-6)	0.1
Poly pharmacy (≥3) (%)	21 (36.8)	167 (48.7)	188 (47)	
Adherence status* (%)				
Adherent	42 (73.7)	205 (59.8)	247 (61.8)	0.04*
Nonadherent	15 (26.3)	138 (40.2)	153 (38.3)	
Duration of treatment (years) (%)				
<1	3 (5.3)	48 (14)	51 (12.8)	0.17
1-5	35 (61.4)	183 (53.4)	218 (54.5)	
>5	19 (33.3)	112 (32.7)	131 (32.8)	

‡Patients not reporting any ADEs. ADEs: Adverse drug events; SD: Standard deviation; *Statistically significant $P < 0.05$

Table 4: Drugs prescribed in the study from various drug classes

Drug class	Drugs prescribed	Percentage of total ADEs (*n*=673)
Antipsychotics	Haloperidol, chlorpromazine, fliphenazine, trifluperazine, thioridazine	72
Second-generation. (atypical) antipsychotics	Olanzapine, quetiapine, clozapine, risperidone, paliperidone, amisulpride, levosulpride and aripiprazole	
Antidepressants	SSRIs (fluoxetine, sertraline), venlafaxine, mirtazepine, imipramine	27
Antimanic agents	Lithium, valproate, carbamazepine	32
Sedatives	Lorazepam, alprazolam, diazepam, nitrazepam, buspirone	44

SSRIs: Selective serotonin reuptake inhibitors; ADEs: Adverse drug events

prescribed trihexyphenidyl. Benzodiazepines were prescribed in 104 (38%) patients. Atypical antipsychotics prescribed in the study [Table 4] were significantly ($P < 0.05$) associated with body weight gain.

Discussion

The prevalence of ADEs in outpatients of mental disorder on psychotropic drugs was found to be 86% in this study. Earlier studies had estimated the overall proportion of outpatients with ADEs to range from 5% to 35%[7,8] but these study data were not from psychiatry practice. Recent

studies have determined that psychiatric medications account for a major proportion of ADEs in inpatients.[9] It is believed that psychiatry practice has certain unique features that should be addressed.[13] Psychiatric patients, especially those in the outpatient setting, may be less adherent to regimens due to lack of insight and denial of illness. A very large proportion of medication prescriptions are for psychiatric medications, and more than one-fourth of all hospital admissions are for psychiatric hospitalizations. Furthermore, psychiatric practice is intensely private, in part because of the need for confidentiality. All these factors may be associated with the high prevalence of ADEs in outpatients of mental disorders. In this study, ADEs were more common in nonadherent patients. It remains to be established whether tolerance to ADEs had failed to develop in nonadherent patients or because of ADEs patients reported nonadherence.

There was no life-threatening or fatal ADEs in the present study. Gandhi *et al*. also reported similar findings in their study on outpatients.[6] In this study, keeping in view the patient's viewpoint, ADEs were categorized according to the patient's self-rated severity. In this study, the majority of ADEs reported were mild. To be more meaningful from the patient's viewpoint, we categorized the ADEs according to the patient's self-rated severity. In this study, majority of the ADEs were mild.

Sedation and weight gain were the most common ADEs in the present study. Although sedation was reported by a large number of patients, majority of them were mild and not necessarily "adverse" and were reported to be helpful in the management to allay aggression or overactivity by the caretakers to some extent. Significantly more patients with schizophrenia and those on antipsychotics reported higher incidence of ADEs than other drugs. Significantly more number of patients on atypical antipsychotics or second-generation antipsychotic medication reported weight gain in the present study, a finding well established in other studies.[14,15]

Conclusion

There is high prevalence of adverse drug events in the outpatients in psychiatric practice in a tertiary care hospital in North India. Because of certain unique features in the psychiatric practice in India, monitoring for adverse drug events in outpatients is imperative for preventive health care. More studies should be planned to establish the prevalence, types, severity and preventability of adverse drug events in outpatients with mental disorders in India.

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Conflicts of interest

There are no conflicts of interest.

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